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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/590,672	10/23/2007	**Andrew Kung**	20363-025 NATL	2840

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EXAMINER	
YAO, LEI	

ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/590,672	KUNG ET AL.	
	Examiner	Art Unit	
	LEI YAO	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 February 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-59* is/are pending in the application.

4a) Of the above claim(s) *14-16, 18-59* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13 and 17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/26/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of invention group I and species melphalan, hyperglycemia, small molecule tyrosine kinase inhibitor, and NVP-AEW541 in the reply filed on 2/23/2009 is acknowledged.

Claims 1-59 are pending.

Claims 18-59 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention and claims 14-16 also are withdrawn from further consideration as non-elected species, there being no allowable generic or linking claim. After review and reconsideration of the elected species of chemotherapeutic agent in claim 17 in light of the prior art, the species doxorubicin is rejoined for examination at this time.

Thus, claims 1-13 and 17, drawn to a method of inhibiting tumor cell growth in a subject comprising administering a chemotherapeutic agent and a composition comprising an IGF-1R inhibitor with species, a small molecule tyrosine kinase inhibitor, NVP-AEW541, in an amount to cause hyperglycemia, melphalan and/or doxorubicin, are examined on the merits.

Information Disclosure Statement

The information disclosure statement (s) (IDS) submitted on5/26/2009 are/is considered by the examiner and initialed copies/copy of the PTO-1449 are/is enclosed.

Specification

1. Specification is objected to because it contains an embedded hyperlink and/or other form of browser-executable code at page 37, line 9, which are improper incorporation by reference. Applicant is required to check entire specification and delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

2. The use of the trademark adriamycin and taxol (page 23, line 1) and acarbose (PRECOSE) and miglitol (GLYSET, page 26, paragraph 2) etc. have been noted in this application. The trademark should be capitalized and with symbol wherever it appears and be accompanied by the generic terminology. For example, GLYSET® (miglitol).

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks. Applicant should check entire application and appropriate corrections are required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 8 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claim recites "the method of claim 2, wherein said preselected period of time is about 1-2 days". There is insufficient antecedent basis for this limitation in the claim

because claim 2 does not contain the recitation or limitation of a preselected period of time. Correction is required. See MPEP 2173.05:

> The lack of clarity could arise where a claim refers to "said lever" or "the lever," where the claim contains no earlier recitation or limitation of a lever and where it would be unclear as to what element the limitation was making reference. Similarly, if two different levers are recited earlier in the claim, the recitation of "said lever" in the same or subsequent claim would be unclear where it is uncertain which of the two levers was intended.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

1. Claims 1-9, 11-12 and 17 are rejected under 35 U.S.C. 102(b) as being anticipated by Kozlowski et al (US Patent No: 6337338, Date of Patent: Jan 2002) as evidenced by Carboni et al (PG Pub. No. US 20050075358 A1, effective filing, Oct 6, 2003) and Doxorubicin Proposed PI Update (FDA Final Approved Label, May 2003).

The claims are drawn to a method of inhibiting tumor cell growth in a subject comprising administering to said subject a chemotherapeutic agent and a composition comprising

an insulin-like growth factor receptor- 1 (IGF-1R) inhibitor, wherein the composition and chemotherapeutic agent is administered at the same time, wherein the composition is administered 48, 24, 12, or 3-12 hours after the chemotherapeutic agent, wherein said composition is administered over a preselected period of time and/or about 1 to 2 days, wherein the dose of said IGF-1R inhibitor or chemotherapeutic is sub-therapeutic, and is in an amount sufficient to cause hyperglycemia (elected), wherein the IGF-1R inhibitor is a small molecule tyrosine kinase inhibitor (elected), and wherein the chemotherapeutic agent is doxorubicin.

In this rejection, an IGF-1R inhibitor is examined to the extent of small molecule tyrosine kinase inhibitor and a chemotherapeutic agent is examined to the extent of doxorubicin in the claimed method.

Kozlowski et al disclose a method of treating and inhibiting tumor cell growth comprising administering a subject a composition comprising an IGF-1R inhibitor in combination with a chemotherapeutic agent (col 6-11; col 7, line 45+ and col 8, line 52+ in particular). Kozlowski et al made the compound heteroaryl-aryl urea having formula I (col 4) that is a small molecule tyrosine kinase IGF-1R inhibitor and inhibits the phosphorylation of IGF-1R kinase and IGF-1 stimulated cell proliferation (col 1, line 46-55; col 6, line 45+; col 13). Kozlowski et al disclose that the two compositions can be administered at the same time or that administering the composition comprising the compound heteroaryl-aryl urea follows the chemotherapy by intervals ranging from minutes to weeks, specifically, 12-24 hours, 6-12 hours, about 12 hours, or 2, 3, 5, 6, or 7 days to weeks (bridging col 7-8), which also meets the limitation of preselected period of time (claim 7-8). Kozlowski et al also disclose that the doses of the IGF-1R inhibitor

used in the method are selected from the range of 0.01 to 1000 mg/kg or 1 to 1000 mg/kg, but will be readily determined by one skilled in the art (col 10, line 24-42). Kozlowski et al disclose the method of combination therapy comprising the chemotherapeutic agent doxorubincin at dose ranging 25-75 mg/m^2 (col 9, line 20-26).

The specification does not teach the dose to cause hyperglycemia recited in claim 11. Hyperglycemia is well defined in the art as a measure of fasting glucose levels that are above 110mg/dl and postprandial glucose levels that above 140 mg/dl (paragraph 14 of Carboni et al). Administration of a small molecule IGF-1R inhibitor at concentration 100mg/kg induces hyperglycemia in the treated patients has been evidenced by Carboni et al (figure 1). Carboni et al specially teach that the IGF-1R inhibitors causing hyperglycemia include the inhibitor of small molecule tyrosine kinase heteroaryl-aryl urea disclosed in the Patent No. 6337338 of Kozlowski et al (paragraph 35, line 6). Thus, in the method of Kozlowski et al above, administration of heteroaryl-aryl urea at a dose ranging 100-1000 mg/kg would cause hyperglycemia, and therefore meet the limitation "in an amount sufficient to cause hyperglycemia" recited in claim 11.

The specification does not teach a dose of sub-therapeutic for a chemotherapeutic agent, but teaches that *A "sub-therapeutic dose" includes doses at which a therapeutic effect of the compound is not detected when the particular compound is administered singularly"* (page 23, paragraph 2-3). The chemotherapeutic drug doxorubicin has been practiced at lower dose (sub-therapeutic dose) in combinational therapy with another anti-cancer agent as evidenced by Doxorubicin Proposed PI Update (FDA for Final Approval label, page 17, May 2003). The Proposed

PI Update provides that for treating a cancer most commonly used dose of doxorubicin is 60-75 mg/m^2 (therapeutic dose) as a single intravenous injection and when used in combination with other drug the most commonly used dosage of doxorubicin is 40-60 mg/m^2. Accordingly, the dose in the combination therapy is sub-therapeutic as compared to the single therapy because it does not produce the same therapeutic effect when it is used alone at this dose. Thus, doxorubicin at any dose ranging 25-40 mg/m^2 or even 40-60 mg/m^2 in the combination therapy disclosed by Kozlowski et al is lower than the therapeutic dose 60-75 mg/m^2, which would not produce a therapeutic effect when it is administered alone and would be considered as a sub-therapeutic dose, therefore, meets the limitation of claim 9: the dose of the chemotherapeutic agent is sub-therapeutic.

2. Claims 1, 7, 10-13 and 17 are rejected under 35 U.S.C. 102(b) as being anticipated by Capraro et al (WO2002092599, published 2002) as evidenced by Carboni et al (PG Pub. No. US 20050075358 A1, effective filing, Oct 6, 2003).

The claims are drawn to a method of inhibiting tumor cell growth in a subject comprising administering to said subject a chemotherapeutic agent (elected) and a composition comprising an insulin-like growth factor receptor- 1 (IGF-1R) inhibitor,wherein said composition is administered over a preselected period of time, wherein the dose of said IGF-1R inhibitor is sub-therapeutic and is in an amount sufficient to cause hyperglycemia (elected), wherein said IGF-1R inhibitor is a small molecule tyrosine kinase inhibitor, NVP-AEW541, or analogs or isomers thereof and chemotherapeutic agent is melphalan or doxorubicin.

In this rejection, an IGF-1R inhibitor is examined to the extent of NVP-AEW541, analogs or isomers thereof (elected species).

The structure NVP-AEW541 is shown in figure 30 of the specification and its chemical name is

7-(3-Azetidin-l-ylmethyl-cyclobutyl)-5-(3-benzyloxy-phenyl)-7H-pyrrolo [2,3-d] pyrimidin-4-ylamine.

Capraro et al disclose a method of inhibiting tumor cell growth comprising administering a subject a composition comprising a small molecule tyrosine kinase IGF-1R inhibitor, NVP-AEW541 or its analogs, in combination with a chemotherapeutic agent (page 1 and 30-36). Capraro et al first made the compound NVP-AEW541 (chemical name in examples 70, page 53; example 110 and 118, page 61 and 64), analogs and isomers thereof having the structure formula I (page 2). Capraro et al disclose that the compounds are IGF-1R tyrosine kinase inhibitor and disclose in vivo method of using the compound in a composition for treating IGF-1R dependent cell proliferation and tumor growth (page 1, 8-9, and 31-33). Capraro et al further disclose the method of treating a subject (human or animal) comprising administering the inhibitor in combination with a chemotherapeutic agent including melphalan (an alkylating agent, page 35 paragraph 2) and doxorubicin (page 34, paragraph 4). Capraro et al also disclose that dose range of the IGF-1R inhibitor for treating tumor growth (neoplastic disease) is 0.1-5g/70kg, preferably 0.5-2g/70kg body weight daily (calculated as 1.42-71.4 mg/kg, and 7.14-38.5mg/kg body weight daily, page 32, last paragraph). Capraro et al also disclose that treatment with the compound states as

soon as the tumor has reached to a volume of 100 mm^3 (page 8, last paragraph), which meets the limitation: the composition is administrated over a preselected period of time (claim 7).

The specification does not teach the dose of the NVP-AEW541 to cause hyperglycemia recited in claim 11. Hyperglycemia is well defined in the art as a measure of fasting glucose levels that are above 110mg/dl and postprandial glucose levels that above 140 mg/dl (paragraph 14 of Carboni et al). Administration of a small molecule IGF-1R inhibitor at concentration above 50 mg/kg (at about 70 mg/kd) induces hyperglycemia in the treated patients has been evidenced by Carboni et al (figure 1). Carboni et al specially teach that the IGF-1R inhibitors include small molecule tyrosine kinase NVP-AEW541 disclosed in the Patent Application of Capraro et al (WO 02/092599) above (paragraph 35, line 7). Thus administration of NVP-AEW541 at a dose 71.4 mg/kg disclosed by Capraro et al above would cause hyperglycemia, therefore, meet the limitation "in an amount sufficient to cause hyperglycemia" recited in claim 11.

Regarding the limitation of claim 10, the dose of IGF-1R inhibitor is sub-therapeutic, the specification teaches an example showing that a sub-therapeutic dose of compound NVP-ADW-742, an analog of NVP-AEW541, is 10 mg/kg (page 46). Thus, the same molecule at a dose below than 10 mg/kg, specifically ranging 1.42-10 mg/kg, used in the method of Capraro et al above meets the limitation “the dose is sub-therapeutic” recited in the claim.

3. Claims 1, 2, 7, 12 and 17 are rejected under 35 U.S.C. 102(e) as being anticipated by Carboni et al (PG Pub No. 20040072760, filed Oct. 2003, priority to Oct. 2002) as evidenced by Wittman et al (PG Pub No. 20040044203, priority to Oct. 2002).

The claims are drawn to a method of inhibiting tumor cell growth in a subject comprising administering to said subject a chemotherapeutic agent and a composition comprising an IGF-1R inhibitor, wherein the composition and chemotherapeutic agent is administered at the same time, wherein said composition is administered over a preselected period of time, wherein said IGF-1R inhibitor is a small molecule tyrosine kinase inhibitor, the chemotherapeutic agent is melphalan or doxorubicin.

Carboni et al disclose a method of treating cancer by inhibiting tumor cell growth comprising administering a subject a pharmaceutical composition comprising an insulin-like growth factor receptor-1 (IGF-1R) inhibitor in combination with a chemotherapeutic agent (paragraph 5, 8-13 and 228). Carboni et al disclose that the IGF-1R inhibitor is a small molecule tyrosine kinase (formula I, paragraph 27 and 228) as evidenced by Wittman et al, who teach that formula I is a tyrosine kinase IGF-1R inhibitor that inhibits phosphorylation of IGF-1R kinase (paragraph 180-181 of Wittman's). Carboni et al disclose that the chemotherapeutic agent used in the method (also called cytotoxic agent) is melphalan or doxorubicin (paragraph 209, 218 and 211). Carboni et al further disclose that the IGF-1R inhibitor can be administered simultaneously to the administration of the chemotherapeutic agent (paragraph 227) and disclose that the times of administration can be modified by the skilled clinician according to established

protocols known in the art (paragraph 230), which reads on administering the composition over a preselected period of time (claim 7).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquires set forth in Graham V. john Deere Co., 383 U.S. 1, 148 USPQ 459 (1996), that are applied for establishing a background for determining obviousness under 25 U.S. 103 (a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or obviousness.

1. Claims 1-13 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kozlowski et al (US Patent No. 6337338, Date of Patent Jan 2002) in view of Capraro et al (WO2002092599, published in 2002) evidenced by Carboni et al (PG Pub. No. US 2005/0075358 A1, effective filing date, Oct 6, 2003) and by Doxorubicin Proposed PI Update (FDA Final Approved Label, May 2003).

The claims are set forth above. In this rejection, the chemotherapeutic agent is examined to the extent of doxorubicin.

The teachings of Kozlowski et al on a method of inhibiting tumor cell growth comprising administering an IGF-1R inhibitor and a chemotherapeutic agent (Doxorubicin), on the dose of the IGF-1R inhibitor in the method that is sufficient to cause hyperglycemia evidenced by Carboni et al, and on the dose of doxorubicin used as sub-therapeutic in the method evidenced by Doxorubicin Proposed PI Update are all set forth above.

Kozlowski et al do not teach the small molecule tyrosine kinase NVP-AEW541, analogs or isomers thereof.

The teaching of Capraro et al on a method of inhibiting tumor cell growth comprising administering an IGF-1R inhibitor, NVP-AEW541, analogs or isomers thereof and a chemotherapeutic agent, on the dose of the compound NVP-AEW541 sufficient to cause hyperglycemia evidenced by Carboni et al, and on the dose of the compound NVP-AEW541 used as sub-therapeutic in the method are also set forth above.

Additionally, Capraro et al teach that the compound of formula I comprising NVP-AEW541 is an unexpected and a potent and selective inhibitor for tyrosine kinase IGF-1R. The diseases having IGF-1R dependent cell proliferations, such as tumor, would have beneficial effects by given the compound (page 1, paragraph 2-3).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to combine the methods of the prior arts to inhibit the IGF-1R dependent tumor growth by replacing the IGF-1R inhibitor of Kozlowski et al with NVP-AEW541 of Capraro et al with expected result. One of ordinary skill in the art

at the time the invention was made would have been motivated to substitute the compound NVP-AEW541 or its analog/isomer for IGF-1R inhibitor in the method of Kozlowski et al in order to benefit for a treatment of a patient having IGF-1R dependent tumor because Capraro et al suggest that compound NVP-AEW541 is a potent and selective inhibitor for IGF-1R that could achieve a therapeutic approach and benefit. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success for combining the teachings to inhibit tumor growth in a patient by administering a composition comprising NVP-AEW541 in combination with a chemotherapeutic agent doxorubicin and would have had a reasonable expectation of success to treat the patient with the schedules or doses as recited in the instant claims because Kozlowski et al have shown the method of combinational therapy with the same treatment schedules and doses, and Capraro et al have also shown a combinational therapy comprising NVP-AEW541 given at a dose of sub-therapeutic and at a dose sufficient to cause hyperglycemia, which are all evidenced by the teachings of Carboni et al and Doxorubicin Proposed PI Update. Therefore, the references in combination teach every limitation of the claims and the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results.

2. Claims 1-10, 12-13, and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kozlowski et al (US Patent No. 6337338, Date of Patent, Jan 2002)

in view of Capraro et al (WO2002092599, published 2002) and Nakamura et al (US Patent No. 6692742, Date of Patent, 2/17/2004, effective filing date 1998).

In this rejection, a chemotherapeutic agent is examined to the extent of melphalan.

The claims are set forth above, wherein the dose of the chemotherapeutic agent, melphalan, is sub-therapeutic.

The teaching of Kozlowski et al on a method of inhibiting tumor cell growth comprising administering an IGF-1R inhibitor and a chemotherapeutic agent are set forth above.

Kozlowski et al do not teach the small molecule tyrosine kinase NVP-AEW541, analogs/isomers thereof and do not teach use of melphalan as a chemotherapeutic agent in the method.

The teachings of Capraro et al on a method of inhibiting tumor cell growth comprising administering an IGF-1R inhibitor, NVP-AEW541, analogs or isomers thereof, at sub-therapeutic dose and melphalan as a chemotherapeutic agent are set forth above and additional teaching on NVP-AEW541 as a potent and selective IGF-1R inhibitor for tumor inhibition is also set forth above.

Capraro et al although teach the sub-therapeutic dose of NVP-AEW541, do not teach the sub-therapeutic dose for melphalan.

The instant specification does not specifically teach a dose of sub-therapeutic for a chemotherapeutic agent, but defines that *A "sub-therapeutic dose" includes doses at*

which a therapeutic effect of the compound is not detected when the particular compound is administered singularly" (page 23, paragraph 2-3).

Nakamura et al teach a method of combination therapy for a cancer comprising administering an anti-cancer antibody and melphalan. Nakamura et al teach that melphalan at 1mg/kg does not achieve the therapeutic benefit when given alone (table 1, line1-3). However, in combination with the antibody, the therapeutic effect is increased by over 40% measured by survival rate (146 days vs.101 days, table I). Thus, melphalan at 1mg/kg does would be considered as a sub-therapeutic dose because when given alone at this dose does not produce a therapeutic effect.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to combine the methods of the prior arts to inhibit a tumor growth in a method of administering NVP-AEW541 and a sub-therapeutic dose of melphalan with expected result. One of ordinary skill in the art at the time the invention was made would have been motivated to substitute new compound NVP-AEW541 for the IGF-1R inhibitor and melphalan at a dose of sub-therapeutic for the chemotherapeutic agent in the method of Kozlowski et al in order to increase the therapeutic efficacy and decrease the cytotoxic effects in a patient having IGF-1R dependent tumor because Capraro et al teach that NVP-AEW541 is a potent and selective inhibitor for IGF-1R, which would achieve a better therapeutic effect and Nakamura et al teach that melphalan at low dose could produce a therapeutic effect in combination with another anticancer agent. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success to arrive

the claimed method with the claimed doses and schedules by combining the teachings because Kozlowski et al have shown a method comprising an IGF-1R inhibitor and a chemotherapeutic agent with different treatment schedules, Capraro et al have shown a method of using the new IGF-1R inhibitor NVP-AEW541 in combination with melphalan, and Nakamura et al have shown the therapeutic effect of using a sub-therapeutic dose of melphalan combined with another anticancer agent. Therefore, the references in combination teach every limitation of the claims and the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lei Yao, Ph.D. whose telephone number is 571-272-3112. The examiner can normally be reached on 8am-6.00pm Monday-Thursday.

Any inquiry of a general nature, matching or file papers or relating to the status of this application or proceeding should be directed to Kim Downing for Art Unit 1642 whose telephone number is 571-272-0521

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Lei Yao/

Examiner, Art Unit 1642

/Larry R. Helms/

Supervisory Patent Examiner, Art Unit 1643